IN THE U.S.PATENT AND TRADEMARK OFFICE

Applicant: DAEWHA PHARM. CO., LTD.
Serial No.: 10/521,669 Art Unit: 1615
Filed: November 8, 2005 Examiners: Jeffrey T. Palenik, and Robert A. Wax
For: Composition for Solubilization of Paclitaxel and Preparation Method Thereof

DECLARATION UNDER 37 C.F.R. SECTION 1.132

Honorable Comissioner of
Patent and Trademarks
Washington, D.C. 20231

I, Hesson Chung, a citizen of Korea, residing at Ssangyon Apt. 3-507, Gwangyo-Dong, Nam-Gu, Incheon 402-715, Korea, hereby declares as follows:

1. I am an inventor of the subject matter of the above identified application.

2. My personal particulars are summarized as follows:

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Principal Research Scientist
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[Education]
BS – Chemistry, Ewha Womans University (1984)
MS – Physical Chemistry, Ewha Womans University (1986)
PhD – Biophysical Chemistry, Ohio State University (1994)

[Research Interests]
Drug delivery systems for insoluble drugs and proteins
Phase behavior of lipids
Cubic and hexagonal mesophases of hydrated lipids

[Book Chapter]
1. Hesson Chung, Seo Young Jeong, Ick Chan Kwon. Cubic liquid crystalline

particles as protein and insoluble drug delivery systems. In Bicontinuous Structured Liquid Crystals. Surfactant Science Series, Eds., Matt Lynch, Patrick Spicer. Marcel Dekker, New York, NY. 2005, p. 349-381.

2. Jonghwi Lee, Gio-Bin Lim, and Hesson Chung, Preparation Methods of Drug Nanoparticles in Pharmaceutical Nanoparticles, Challa Kumar Ed. Wiley, Denmark, 2005, p. 255-286.

[Papers]

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2. Joon Woo Park, Hesson Chung. Studies on the formation and stability of colloids (I): Perturbation of micelle formation of sodium deoxycholate by amides. **Bull Kor Chem Soc** 1986;7:399-402.

3. Joon Woo Park, Hesson Chung. Aggregation and dissolution of cationic dyes with an anionic surfactant. **Bull Kor Chem Soc** 1986;7:113-116.

4. Hesson Chung, Martin Caffrey. Directcorrelation of structure changes and thermal events in hydrated lipid established by simultaneous calorimetry and time-resolved x-ray diffraction. **Biophys J** 1992;63:438-447

5. Hesson Chung, Martin Caffrey. The neutral area surface of the cubic mesophase: location and properties. **Biophys J** 1994;66:377-381.

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7. Hesson Chung, Martin Caffrey. Polymorphism, mesomorphism, and metastability of monoelaidin in excess water. **Biophys J** 1995;69:1951-1963.

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9. Sun Woo Yi, Tae Young Yun, Tae Woo Kim, Hesson Chung, Young Wook Choi, Ick Chan Kwon, Eunhee Bae Lee, Seo Young Jeong. A cationic lipid emulsion/DNA complex as a physically stable and serum-resistant gene delivery system. **Pharm Res** 2000;17:314-320.

10. Tae Woo Kim, Hesson Chung, Ick Chan Kwon, Ha Chin Sung, Seo Young Jeong. In vivo gene transfer to the mouse nasal cavity mucosa using a stable cationic lipid emulsion. **Mol Cell** 2000;10:142-147.

11. Tae Woo Kim, Hesson Chung, Ick Chan Kwon, Ha Chin Sung, Seo Young Jeong. Optimization of lipid composition in cationic emulsion as in vitro and in vivo transfection agents. **Pharm Res** 200118:54-60.

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Kim, Ick Chan Kwon, Hesson Chung, Seo Young Jeong. Structural characteristics of size controlled self-aggregates of deoxycholic acid-modified chitosan and their application as a DNA delivery carrier. **Bioconjugate Chem** 2001;12:932-938.

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15. Hesson Chung, Ji-seon Kim, Jung Yoon Um, Ick Chan Kwon, Seo Young Jeong. Self-assembled "nanocubicle" as a carrier for peroral insulin delivery. **Diabetologia** 2002;45:448-451.

16. Tae Woo Kim, Young Jin Kim, Hesson Chung, Ick Chan Kwon, Ha Chin Sung, Seo Young Jeong. The role of non-ionic surfactanst on cationic lipid mediated gene transfer. **J Cont Rel** 200282:455-465.

17. Jun-Young Seo, Seung Yong Seong, Byung-Yoon Ahn, Ick Chan Kwon, Hesson Chung, Seo Young Jeong. Cross-protective immunity of mice induced by oral immunization with pneumococcal surface adhesin A encapulated in microspheres. **InfectionImmun** 2002;70:1143-1149.

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20. Li-Qiang Zheng, Jung Yoon Um, Hesson Chung, Ick Chan Kwon, Gan-Zuo Li, Seo Young Jeong. Microstructure of dispersed colloidal particles of a bilayer cubicphase. **J Dispersion Sci Tech** 2003;24:123-128.

21. Young Jin Kim, Tae Woo Kim, Hesson Chung, Ick Chan Kwon, Ha Chin Sung, Seo Young Jeong. The effects of serum on the stability and the transfection activity of the cationic lipid emulsion with various oils. **Int J Pharm** 2003;252:241-252.

22. Jung Yoon Um, Hesson Chung, Kil Soo Kim, Ick Chan Kwon, Seo Young Jeong. In vitro cellular interaction and absorption of dispersed cubic particles. **Int J Pharm** 2003;253:71-80.

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25. Sung Eun Kim, Jae Hyung Park, Yong Woo Cho, Hesson Chung, Seo Young Jeong, Eunhee Bae Lee, Ick Chan Kwon. Porous chitosan scaffold containing

microspheres loaded with transforming growth factor-1: Implications for cartilage tissue engineering. **J Control Release** 2003;91:365-374.

26. Yong Woo Cho, Jae Hyung Park, Sanghee Kim, Yong-Hyun Cho, Joong Myung Choi, Hee Jong Shin, You Han Bae, Hesson Chung, Seo Young Jeong, Ick Chan Kwon. Gentamicin-releasing urethral catheter for short-term catheterization. **J Biomater Sci Polym Edn** 200314:963-97.

27. Jae Hyung Park, Yong Woo Cho, Joong Myung Choi, Hee Jong Shin, You Han Bae, Hesson Chung, Seo Young Jeong, Ick Chan Kwon. Norfloxacin-releasing urethral catheter for long-term catheterization. **J Biomater Sci Polym Edn** 2003;14:951-962.

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29. Sang Cheon Lee, Chulhee Kim, Ick Chan Kwon, Hesson Chung, Seo Young Jeong. Polymeric micelles of poly(2-ethyl-2-oxazoline)-block-poly (-caprolactone) copolymer as a carrier for paclitaxel. **J Cont Rel** 2003;89:437-446.

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37. Jung Wan Hong, Jae Hyung Park, Kang Moo Huh, Hesson Chung, Ick Chan Kwon, Seo Young Jeong. PEGylated polyethylenimine for *in vivo* local gene delivery

based on lipiodolized emulsion system. **J Cont Rel** 2004;99:167-176.

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39. Kwangmeyung Kim, Jong-Ho Kim, Sungwon Kim,Hesson Chung, Kuiwon Choi, Ick Chan Kwon. Self-Assembled Nanoparticles of Bile Acid-Modified Glycol Chitosans and Their Applications for Cancer Therapy. **Macromolecular Research** 2005;13:167-175.

40. Hyuk Sang Yoo, Jung Eun Lee, Hesson Chung, Ick Chan Kwon, Seo Young Jeong. Self-assembled nanoparticles containing hydrophobically modified glycol chitosan for gene delivery. **J Cont Rel** 2005;103:235-243.

41. In-Hyun Lee, Yeong Taek Park, Kyungho Roh, Hesson Chung, Ick Chan Kwon, Seo Young Jeong. Stable paclitaxel formulations in oily contrast medium. **J Cont Rel** 2005;102:415-425.

[Granted Patents]

1. Anti-cancer drug-chitosan complex forming self-aggregates and preparation method thereof (KR 0507968)
2. Paclitaxel mixed composition and water-in-oil type emulsion formulation for chemoembolization and preparation method thereof (KR0497258)
3. Emulsion agent using iodized oil with cationic polymers as an efficient carrier for physiologically active materials or drug and preparation method thereof (KR0428418)
4. Composition for solubilization of paclitaxel and preparation method thereof (KR0533458)
5. Paclitaxel composition for the intravesical treatment of bladder tumor and preparation method thereof (KR0573289)
6. P-glycoprotein inhibitor comprising octilonium bromide as an effective ingredient (KR503889)
7. Mucoadhesive composition and formulation for solubilization of insoluble drugs and preparation method thereof (KR0533460)
8. Iodized oil emulsion as an efficient physiologically active materials or drug carrier and preparation method thereof (KR0505434)
9. Oily paclitaxel composition and formulation for chemoembolization and preparation method thereof (KR0539451)
10. Chitosan complex having hydrophobic moiety and preparation method thereof (KR0503293)
11. Lipid emulsion and solid lipid nanoparticle as a gene or drug carrier (KR0342835)
12. Formulation solubilizing water-insoluble agents and preparation method thereof (US6994862, AU777347, CN1189215)
13. Solid lipid nanoparticle as a gene or drug carrier, formulation, and method for

preparation thereof (KR0374482)

14. Formulation for oral delivery of insulin and preparation method thereof (KR0508695)

15. Injectable Gel Type Lipid Composition And Preparation Method Thereof (KR0426636)

16. Composition, liquid formulation, and powder formulation for enhancing solubility of PsaA, manufacturing method thereof and vaccine (KR0406503)

[Invited Talks]

1. The curvature elastic energy function of the cubic mesophase. March Annual Meeting. American Physical Society, 1994 Pittsburgh, PA

2. Lipid microstructures as drug delivery systems. Korean Pharmaceutical Society, 9th Science Month DDS Symposium, 1997 Seoul, Korea.

3. Cubosome precursor formulations: new lipid-based drug delivery systems. Korean Pharmaceutical Society, 12th Science Month DDS Symposium, 2000 Seoul, Korea.

4. Nanostructures in Polymer-Lipid Systems. Korean Polymer Society, Spring Meeting, 2003 Seoul, Korea.

5. Optical Imaging. Korean Society for Therapeutic Radiology And Oncology, 21th Annual Meeting, 2003 Seoul, Korea.

3. I am thoroughly familiar with the Office Action dated December 11, 2009, wherein claims 1, 5, 6, 10-13, 27, 72, 73 and 75-78 of the present application have been rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. (USPN 6,531,139).

In the Office Action, the Examiner concluded that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary. In this connection, I have conducted precipitation tests of the formulation of Gao et al. using the Example 44 of Gao et al.

4. Under my direction and control, a series of precipitation tests were conducted for determining that i) the formulation of Gao et al. could not be used for formulation of Paclitaxel; and ii) diolein could affect the composition of the present invention.

(1) Preparation of Test Samples

The example 44 of Gao et al. was made exactly in accordance with the description of Gao et al. The contents are shown in the following Table 1:

Table 1.

Component	Weight (mg/g)	% W/W
Paclitaxel	60	6
EtOH/PEG400 (1:1)	300	30
Cremophor EL	440	44
Diolein/monoolein (8:2)	200	20

(2) Test Method

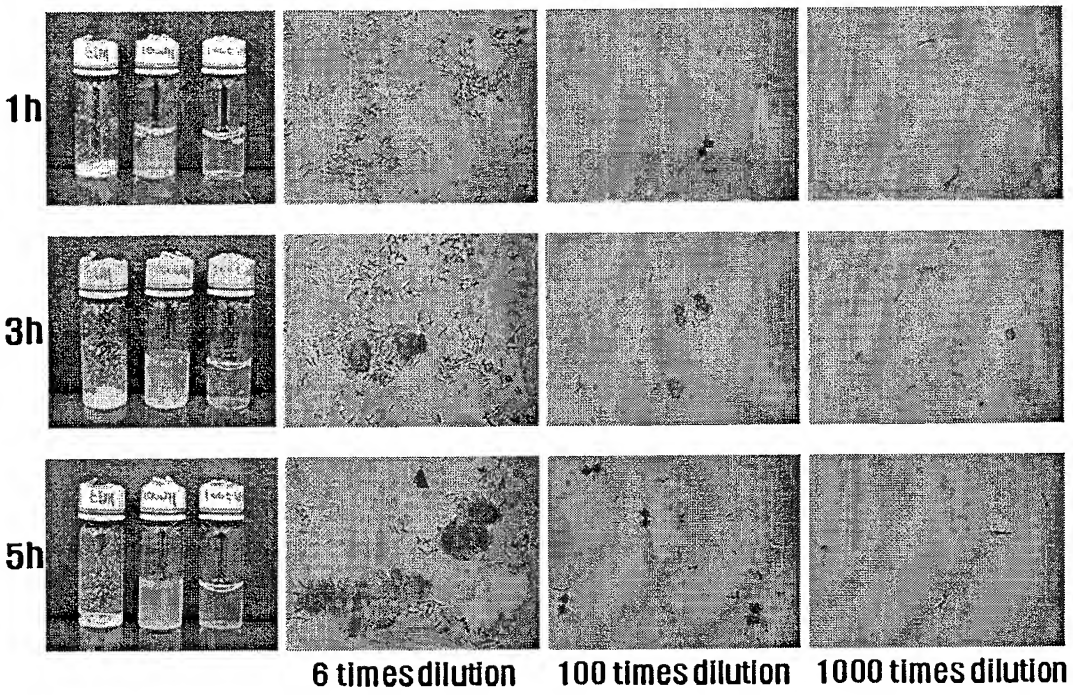
Example 44 of Gao et al. was diluted with distilled water to observe whether paclitaxel precipitation would be observed. Example 44 was diluted 6 times, 100 times, and 1000 times, respectively. After dilution with distilled water, vortexing was carried out for 30 seconds.

The individual samples were kept under normal conditions. After 1, 3 and 5 hours, each of the samples were observed under a microscope to identify whether Paclitaxel precipitation had occurred.

(3) Test Results

1) The results of the precipitation tests of the Example 44 of Gao et al. are shown in Figure 1 below, which is observed under microscopy.

Figure 1.



As shown in Figure 1, Paclitaxel precipitation was observed in all samples. Paclitaxel was precipitated into needle type crystals. In particular, as soon as the compound was diluted, Paclitaxel precipitation was observed in case of 6 and 100 times dilutions.

5. Conclusion

1) When a formulation of a drug is administered to the human body, the formulation cannot help coming into contact with biological fluids. In particular, in the case of a water-insoluble drug such as Paclitaxel, the formulation of the drug still should be able to solvate Paclitaxel without precipitation when coming into contact with biological fluids. Aggregated paclitaxel does not have any pharmacological effect since it cannot be absorbed or delivered into the target site of the body. This is even more important in the case of an oral formulation, because the formulation comes into contact with saliva as soon as it is administered and is mixed with intestinal fluid later on. To evaluate this, an experiment bringing into contact the formulation with water is useful, because biological fluids are mainly composed of water. In this light, if the precipitation of a drug occurs when the formulation of the drug is put in contact with water, such formulation is not a suitable candidate for formulation of the drug. From the results in the above, the formulation of Gao et al. is not useful as a formulation of Paclitaxel. Even though Gao et al. describes a formulation of Paclitaxel as in Example 44, the

precipitation of Paclitaxel after contact with water shows that bioavailability of Gao's formulation would be far below than that of the present invention, and the present invention has substantially superior effect to Gao et al.

2) Diolein of Gao et al. clearly affects the present composition, because the main difference between the present invention and Gao et al. is diolein. Example 44 which contains diolein could not be used for an oral formulation of Paclitaxel from the above result, so the term "consisting essentially of" of the claims of the present application means that diolein could not be included.

3) To fall within the present invention from Gao et al., i) diolein should be exchanged with triglyceride/oil and ii) the solvent should be excluded from Gao et al. Such components are essential to Gao et al., so such modification is substantially impossible. Furthermore, iii) Gao et al. teaches a mixture of diglyceride and monoglyceride in a ratio of from 9:1 to 6:4, which is distinct from the present invention

6. I hereby declare that all statements made herein are to my own knowledge true and these statements are made on the best information and are believed to be true; further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize that validity of the application or any patents issuing thereon.

Dated: 19th day of May 2010

Signature: 

Hesson Chung